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CONTRAST AGENT

Field of invention

The present invention relates to diagnostic contrast agents suitable for use in diagnostic imaging techniques in which a disease state may be imaged using such contrast agents. More particularly the invention relates to contrast agents in which the targeting vector binds to angiotensin II reseptors.

Background of invention

Angiotension II (hereinafter AII) is an octapeptide (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe) which is the primary active species in the renin-angiotensin aldosterone system (the RAS system) which regulates blood pressure and electrolyte and water balance. The RAS system is illustrated schematically in Figure 1 hereto which is based on Figure 1 in the article by Foote et al. in Ann. Pharmacother. 27: 1495-1503 (1993).

AII exerts its biological effects via interaction with specific receptors present in many tissues in the human or animal body (eg. blood vessels, heart, brain, liver, kidney, uterus and ovary). While one of its major effects is to promote vasoconstriction, AII has several other effects that lead to increased blood pressure and sodium retention. Thus, for example, in response to stimulation of AII receptors in the adrenal cortex, aldosterone is released and this stimulates sodium and water retention and potassium excretion in the distal tubules and cortical collecting ducts of the kidney. AII also has a direct effect on the kidney including glomerular hypertrophy and increased proximal tubule sodium reabsorption. Furthermore, AII acts centrally to stimulate thirst and enhance antidiuretic hormone release thereby leading to increased intravascular volume.

Accordingly, suppression of AII's effects has been used therapeutically, for example in the management of hypertension and congestive heart failure. This has been achieved in a number of ways: by the use of renin inhibitors which block the conversion of angiotensinogen to angiotensin I (the precursor to AII); by the use of angiotensin converting enzyme (ACE) inhibitors that block the conversion of angiotensin I to AII (and also block bioconversion of bradykinin and prostaglandins); by the use of anti-AII-antibodies; and by the use of AII-receptor antagonists.

It has been found that different types of AII receptors (binding sites) exist within the body and that AII binding has different effects at different binding sites. Thus the AT1 receptor mediates the major cardiovascular action of the RAS and is inhibited by the

AII-receptor antagonists Losartan and DTT, while the other major receptor family, AT2, is inhibited by PD 123177 and its structural analogs. Other receptors for AII besides AT1 and AT2 are known and are generally referred to as $AT_{atypical}$ (see Kang et al., Am. Heart J. 127: 1388-1401 (1994)).

It has been found that it is possible to image AII receptor sites in vivo using targeted contrast agents in which the targeting vector has affinity for AII-receptor sites. The AII receptors are generally located within the cardiovascular system and are accessible to such contrast agents when they are administered into the blood stream. Accordingly, using such targeted contrast agents it is possible to detect diseases and disorders such as heart failure, atherosclerosis and restricted blood flow, as well as other vascular diseases and disorders, and also to monitor the progression of treatment for such diseases and disorders.

WO 98/18496 discloses 123I and 131I labelled Losartan for in vivo imaging, and US 5,264,581 (Cariani) discloses radioiodinated imidazole Angiotensin II antagonists, (e.g. Losartan).

The present invention

It has now been found that AII-receptor antagonists such as e.g. Losartan, Valsartan, Candesartan and Eprosartan labelled with an imaging moiety are useful diagnostic imaging agents for in vivo imaging of a human or animal body.

The contrast agents of the present invention are useful for the in vivo diagnostic imaging of chronic heart failure.

Detailed Description of the Invention

In a first aspect, the present invention provides a contrast agent as defined by formula I,

V-L-R (Formula I)

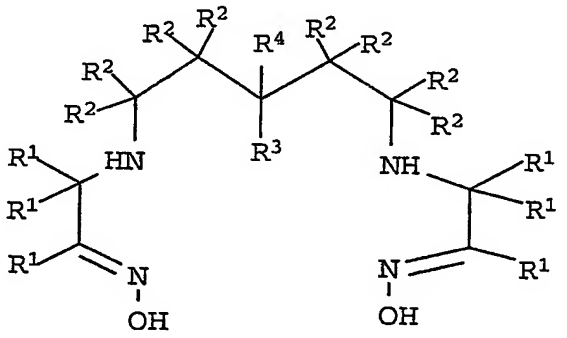
wherein V is a vector having affinity for the AII-receptor, L represents a bond, a spacer or linker and R represents a chelating agent or a reporter moiety.

The role of the linker L is to couple vector to reporter, and in the case where L is a spacer moiety the role of L is to distance the relatively bulky chelating agent from the active site of the vector,V.

A linker moiety may serve to link one vector to one reporter; alternatively it may link together more than one vector and/or more than one reporter. Likewise a reporter or a vector may be linked to more than one linker. Use in this way of a plurality of reporters (e.g. several linker-reporter moieties attached to one vector or several reporters attached to one linker itself attached to one vector) may enable the detectability of the contrast agent to be increased (e.g. by increasing its radioopacity, echogenicity or relaxivity) or may enable it to be detected in more than one imaging modality. Use in this way of a plurality of vectors may e.g. increase the targeting efficiency of a contrast agent or may make the contrast agent/therapeutic agent able to target more than one site, e.g. different receptors for an agent which has receptor heterogeneity.

The linker moiety L may be a simple bond, PEG units, PEG-like linkers or may be represented by other linkers well known in the art, e.g. as described in WO 01/77145 pages 23-27, the content of which are incorporated herein by reference.

R may be represented by a chelating agent of Formula II

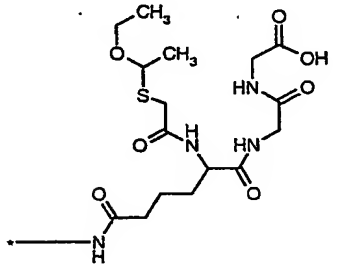


(II)

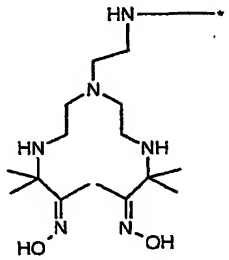
where:

each R^1, R^2, R^3 and R^4 is independently an R group;

each R group is independently H or C_{1-10} alkyl, C_{3-10} alkylaryl, C_{2-10} alkoxyalkyl, C_{1-10} hydroxyalkyl, C_{1-10} alkylamine, C_{1-10} fluoroalkyl, or 2 or more R groups, together with the atoms to which they are attached form a carbocyclic, heterocyclic, saturated or unsaturated ring, or can represent a chelating agent given by formulas a, b, c and d.



a



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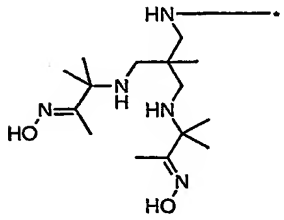
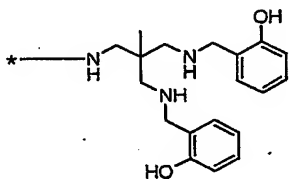
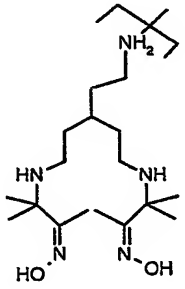


c



d

A preferred example of a chelating agent is represented by formula e.



e

Conjugates comprising chelating agents of Formula II can be radiolabelled to give good radiochemical purity, RCP, at room temperature, under aqueous conditions at near neutral pH. An advantage of radiolabelling the conjugates at room temperature is a simplified procedure in a hospital pharmacy.

However the compounds defined in Formula I may also comprise chelating agents, R, as defined in WO 01/77145, Table I, pages 11-15.

In some aspects of the invention, R comprises a reporter moiety where said reporter moiety comprises a radionuclide. Further definitions of chelating agents are listed in WO 01/77145,Table I, pages 11-15, the content of which are incorporated herein by reference.

The reporter moieties (R) in the contrast agents of the invention may be any moiety capable of detection either directly or indirectly in an in vivo diagnostic imaging procedure.

For MR imaging the reporter will either be a non zero nuclear spin isotope (such as ^{19}F) or a material having unpaired electron spins and hence paramagnetic, superparamagnetic, ferrimagnetic or ferromagnetic properties; for light imaging the reporter will be a light scatterer (e.g. a coloured or uncoloured particle), a light absorber or a light emitter; for magnetometric imaging the reporter will have detectable magnetic properties; for electrical impedance imaging the reporter will affect electrical impedance; and for scintigraphy, SPECT, PET, and the like, the reporter will be a radionuclide.

Stated generally, the reporter may be (1) a chelatable metal or polyatomic metal-containing ion (i.e. TcO, etc), where the metal is a high atomic number metal (e.g. atomic number greater than 37), a paramagentic species (e.g. a transition metal or lanthanide), or a radioactive isotope, (2) a covalently bound non-metal species which is an unpaired electron site (e.g. an oxygen or carbon in a persistant free radical), a high atomic number non-metal, or a radioisotope, (3) a polyatomic cluster or crystal containing high atomic number atoms, displaying cooperative magnetic behaviour (e.g. superparamagnetism, ferrimagnetism or ferromagnetism) or containing radionuclides.

Examples of particular preferred reporter groups (R) are described in more detail below.

Chelated metal reporters are preferably chosen from the group below; ^{90}Y, ^{99m}Tc, ^{111}In, ^{47}Sc, ^{67}Ga, ^{51}Cr, ^{177m}Sn, ^{67}Cu, ^{167}Tm, ^{97}Ru, ^{188}Re, ^{177}Lu, ^{199}Au, ^{203}Pb and ^{141}Ce.

The metal ions are desirably chelated by chelant groups on the linker moiety. Further examples of suitable chelant groups are disclosed in US-A-4647447, WO89/00557, US-A-5367080, US-A-5364613.

Methods for metallating any chelating agents present are within the level of skill in the art. Metals can be incorporated into a chelant moiety by any one of three general methods: direct incorporation, template synthesis and/or transmetallation. Direct incorporation is preferred.

Thus it is desirable that the metal ion be easily complexed to the chelating agent, for example, by merely exposing or mixing an aqueous solution of the chelating agent-containing moiety with a metal salt in an aqueous solution preferably having a pH in the range of about 4 to about 11. The salt can be any salt, but preferably the salt is a water soluble salt of the metal such as a halogen salt, and more preferably such salts are selected so as not to interfere with the binding of the metal ion with the chelating agent. The chelating agent-containing moiety is preferrably in aqueous solution at a pH of between about 5 and about 9, more preferably between pH about 6 to about 8. The chelating agent-containing moiety can be mixed with buffer salts such as citrate, carbonate, acetate, phosphate and borate to produce the optimum pH. Preferably, the buffer salts are selected so as not to interfere with the subsequent binding of the metal ion to the chelating agent.

The following isotopes or isotope pairs can be used for both imaging and therapy without having to change the radiolabelling methodology or chelator: $^{47}Sc_{21}$; $^{141}Ce_{58}$; $^{188}Re_{75}$; $^{177}Lu_{71}$; $^{199}Au_{79}$; $^{47}Sc_{21}$; $^{131}I_{53}$; $^{67}Cu_{29}$; $^{131}I_{53}$ and $^{123}I_{53}$; $^{188}Re_{75}$ and $^{99m}Tc_{43}$; $^{90}Y_{39}$ and $^{87}Y_{39}$; $^{47}Sc_{21}$ and $^{44}Sc_{21}$; $^{90}Y_{39}$ and $^{123}I_{53}$; $^{146}Sm_{62}$ and $^{153}Sm_{62}$; and $^{90}Y_{39}$ and $^{111}In_{49}$.

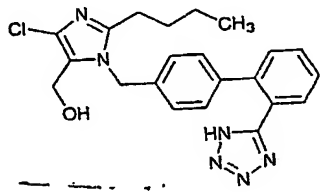
Preferred non-metal atomic reporters include radioisotopes such as ^{18}F as well as non zero nuclear spin atoms such as ^{19}F, and heavy atoms such as I.

In a further embodiment of this invention, the use of radioisotopes fluorine is specifically contemplated. For example, if the vector V or linker L is comprised of substituents that can be chemically substituted by fluorine in a covalent bond forming reaction, such as, for example, substituents containing hydroxyphenyl or p-nitrobenzoyl functionality, such substituents can be labelled by methods well known in the art with a radioisotope of fluorine. These species can be used in therapeutic and diagnostic imaging applications. While, at the same time, a metal attached to a

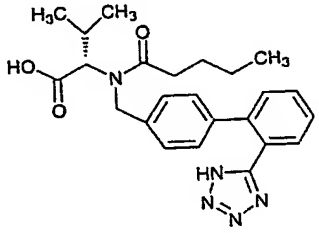
chelating agent on the same vector-linker can also be used in either therapeutic or diagnostic imaging applications.

The reporter moiety R may also represent a chromophore to be used in light imaging procedure. By chromophore is meant a group in a composition of matter, e.g. an organic or inorganic group which absorbs and/or emits light. By light is meant electomagnetic radiation having wavelengths from 300-1300 nm. Chromophores having absorpsion and/or emission maxima in the visible to far infrared range are particularly relevant.

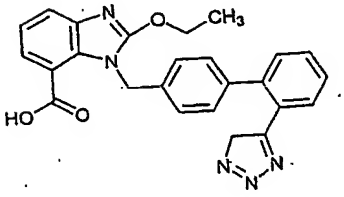
The invention may be exemplified by Losartan derivatives and is based on attchment of Linker and reporter moieties to the imidazol 5-position. The prinsiple also applies to other compounds having structural similarities, e.g. Valsartan, Candesartan and Eprosartan, possessing suitable anchoring sites in the part of the molecule corresponding to the Losartan imidazole ring.



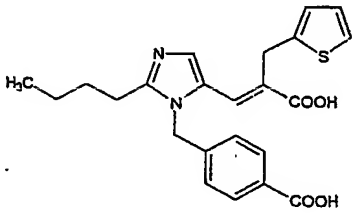
Losartan



Valsartan

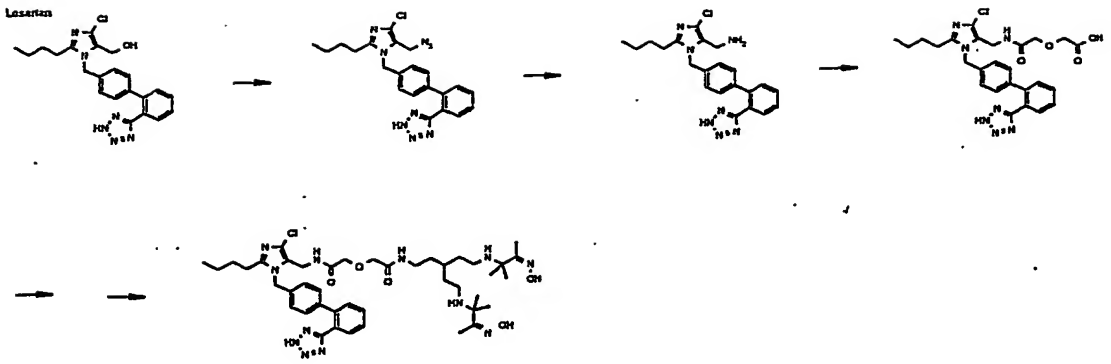


Candesartan



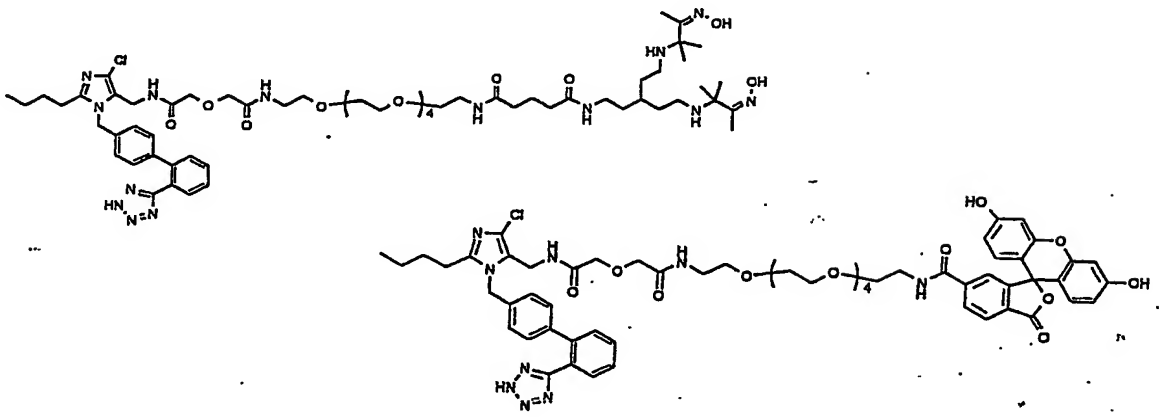
Eprosartan

Scheme 1 shows an example of how the imidazole 5-position can be used to anchor a chelating agent of formula e to give a derivatised Losartan molecule for Tc-chelation. Parent Losartan molecule is transformed to the azide-derivative followed by reduction to the corresponding amine. The amine is reacted with diglycolic anhydride, followed by activation and reaction with a suitable derivative of the chelating agent of formula e.



Scheme 1

Other examples of related structures are shown below;



The present invention also provides a pharmaceutical composition comprising an effective amount (e.g. an amount effective for enhancing image contrast in in vivo imaging) of a compound of general formula I or a salt thereof, together with one or more pharmaceutically acceptable adjuvants, excipients or diluents.

Viewed from a further aspect the invention provides the use of a compound of formula I for the manufacture of a contrast medium for use in a method of diagnosis involving administration of said contrast medium to a human or animal body and generation of an image of at least part of said body.

Viewed from a still further aspect the invention provides a method of generating enhanced images of a human or animal body previously administered with a contrast agent composition comprising a compound as defined by formula I, which method comprises generating an image of at least part of said body.

Claims

1. A compound of the general formula I:

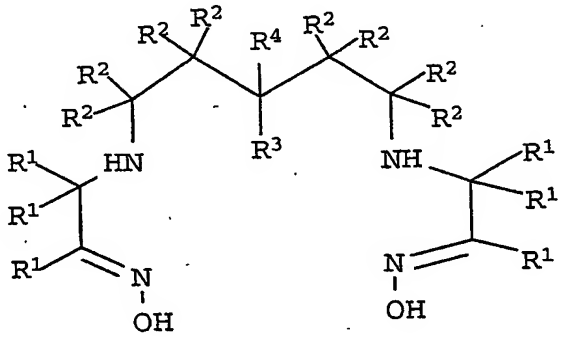
V – L – R Formula I

or pharmaceutically acceptable salt thereof, wherein V is an Angiotensin II receptor antagonist or derivatives thereof, L is a bond or a linker moiety and R is an imaging moiety, a chelating agent or a reporter moiety

2. A compound according to claim 1 wherein V is Losartan, Valsartan, Candesartan, Eprosartan or derivatives thereof.

3. A compound according to claims 1 and 2 wherein R represents a chelating agent or a reporter moiety

4. A compound as claimed in any of the previous claims where R is a chelating agent of Formula II



(II)

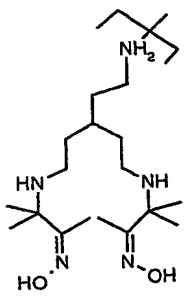
where:

each R^1, R^2, R^3 and R^4 is independently an R group;

each R group is independently H or C_{1-10} alkyl, C_{3-10} alkylaryl, C_{2-10} alkoxyalkyl, C_{1-10} hydroxyalkyl, C_{1-10} alkylamine, C_{1-10} fluoroalkyl, or 2 or more R groups, together with the atoms to which they are attached form a carbocyclic, heterocyclic, saturated or

unsaturated ring.

5. A compound as claimed in any of the previous claims where R is



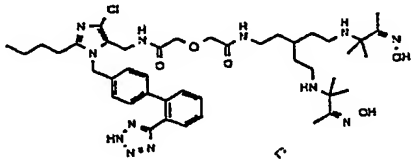
e

6. A compound as claimed in any of the previous claims wherein R comprises a reporter moiety.

7. A compound as claimed in claim 6 wherein the reporter moiety comprises metal radionuclides, paramagnetic metal ions, fluorescent metal ions, choromophores, heavy metal ions or cluster ions.

8. A compound as claimed in claims 6 and 7 wherein the reporter moiety comprises ^{90}Y, ^{99m}Tc, ^{111}In, ^{47}Sc, ^{67}Ga, ^{51}Cr, ^{177m}Sn, ^{67}Cu, ^{167}Tm, ^{97}Ru, ^{188}Re, ^{177}Lu, ^{199}Au, ^{203}Pb, ^{141}Ce or ^{18}F.

9. A compound as claimed in claim 1 defined by the following formula:



10. A compound as claimed in claims 1-9 wherein the reporter moiety is ^{99m}Tc.

11. A pharmaceutical composition comprising an effective amount of a compound of general Formula (I) or a salt thereof, together with one or more pharmaceutically acceptable adjuvants, excipients or diluents for use in enhancing image contrast in *in vivo* imaging or for treatment of a disease.

12. Use of a compound as claimed in any one of claims 1 to 10 in the preparation of a contrast medium for use in a method of diagnosis involving administering said contrast medium to a human or animal body and generating an image of at least part of said body.

13. A method of generating images of a human or animal body involving administering a contrast agent to said body, and generating an image of at least a part of said body to which said contrast agent has distributed, characterised in that said contrast agent comprises a compound as claimed in any one of claims 1 to 10.

14. A method of generating enhanced images of a human or animal body previously administered with a contrast agent composition comprising a compound as claimed in claims 1 to 10, which method comprises generating an image of at least part of said body.

Abstract

The present invention relates to a contrast agent of Formula I

V – L – R Formula I

where V is an Angiotensin II receptor antagonist or derivatives thereof, L is a bond or a linker moiety and R is an imaging moiety, a chelating agent or a reporter moiety

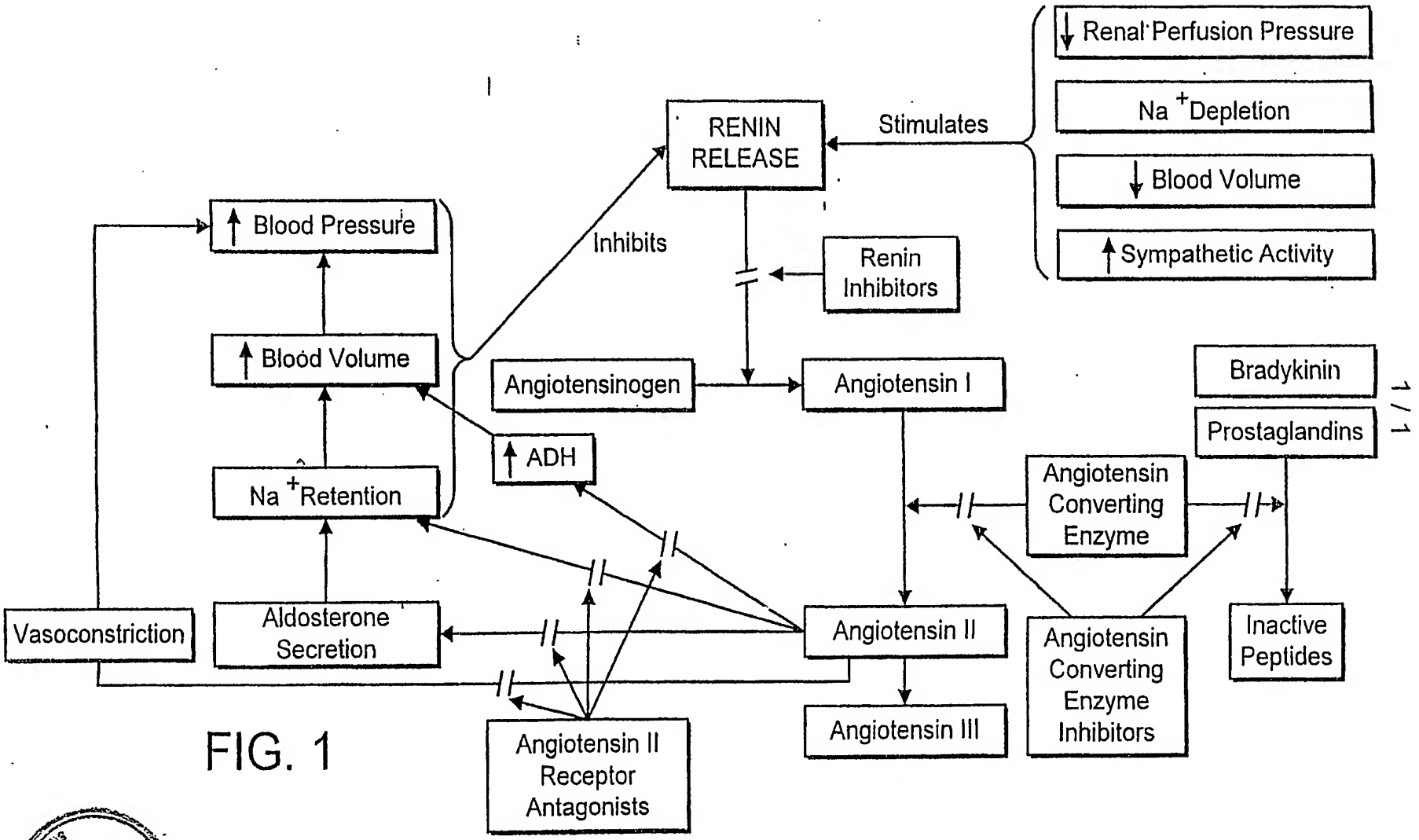


FIG. 1